An Electrochemical Perspective Of the Function of GC-rich Domains Flanking Human Genes: Protection Against Oxidation

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GC-rich domains flank transcribed genes of the human genome.[1,2] The genomic,[1,2] physical,[3,4] intracellular-chemical [5] and electrochemical data published in the past two months are consistent with the suggestion that the GC-rich domains flanking the human genes serve to cathodically protect these against transient oxidative damage.[6] According to the suggestion, the GC-rich domains are sacrificially oxidized, absorbing the transient damage until it is recognized, excised and repaired. Nearly simultaneously with the publication of the human genome, Kasumov and his colleagues [3] confirmed the measurements of Fink and Schönenberger,[4] proving that carriers (electrons or holes) are conducted across gene-sized, 0.6 μm long DNA domains. A few weeks earlier Amatore et al. reported that the transient concentrations of strong oxidizers exemplified by nitric oxide, capable of oxidizing DNA, reaches in stimulated fibroblasts 0.4 mM.[5] This intracellular concentration corresponds to 10^{14} nitric oxide molecules per copy of the genome. A few months earlier May et al. have shown that nitric oxide permeates rapidly through the lipid bilayer membrane of red blood cells,[7] making it unlikely that the nuclear lipid bilayer membrane shields genes from nitric oxide. At the same time, the now proven carrier conduction makes it likely that genes at rest are cathodically protected against oxidation: The genes' flanking GC-rich domains are electrochemically reducing relative to the more noble AT-richer genes.[8] As a result, a hole injected by an oxidant into the electronically conducting gene does not oxidize the gene, but oxidizes instead the gene's flanking GC-rich region.[6]

The measured $>10^3\ \Omega^{-1}\ cm^{-1}$ conductivity along the main axis of the double helices exceeds 1 % of the $10^5\ \Omega^{-1}\ cm^{-1}$ conductivity of steel.[3,4] Unlike in large band gap semiconductors, it drops only little upon cooling from 300ºK to 1ºK. Below 1ºK the DNA is superconducting.[4] Experiments in which solid and aligned DNA appeared to be semiconducting or insulating are now explained by the electrical contacts used in these. For the experiments to be definitive, the contacts must be ohmic and must not affect the measurements.[4] When DNA is dissolved in an aqueous solution it retains only a fraction of its conductivity. Carriers are transferred only across ~50 base pairs, and GC-sequences are preferentially oxidized within the oligonucleotide only when the carriers traverse fewer than 50 base pairs. [9]

Electrochemists and materials scientists have known for over a century that when two electron or hole conductors are in an oxidizing environment, are immersed in the same electrolytic solution and are in electronic contact with each other, then the more noble of the two metals is protected against oxidation, while the less noble metal is sacrificially oxidized. The protective process is known as cathodic protection. When oxygen attacks the more noble metal, it captures an electron and a hole is injected. The hole drifts to, and is captured by, the more reducing metal, oxidizing it. The electrical resistance of the contacted electrodes determines the distance across which protection is effective. Hulls of ships, pipelines, bridges and storage tanks are cathodically protected against oxidative corrosion. A ship carries a sea water-immersed zinc rod, attached through a copper cable to its steel hull. In the electrochemical cell formed the more reducing zinc [$Zn \rightarrow Zn^{2+} + 2e^-$, E^0 = -0.76 V (SHE)] is a sacrificially oxidized anode and the more noble iron [$Fe \rightarrow Fe^{2+} + 2e^-$, E^0 = -0.41 V (SHE)] is a protected cathode. Oxidation of the steel is prevented by the thermodynamically spontaneous reaction $Fe^{2+} + Zn \rightarrow Fe + Zn^{2+}$. Just as the redox potential of zinc is reducing by about 0.3 V relative to that of iron, the redox potential of G is reducing by about 0.3 V relative to T, A and C (G, 1.04 ; T, 1.29; A, 1.32; and C, 1.44 V vs. NHE and at pH 7).[8] The gene-flanking GC-rich domains are thus sacrificially oxidizable microanodes and the GC-poorer genes are protected microcathodes. Not only is G the most reducing of the bases, but its catalytic one-electron oxidation kinetics in poly-GC sequences is particularly rapid.[10] The oxidative damage can thus be shifted from the transcribed, more noble gene to the flanking, non-transcribed, GC-rich domain.[6]

A gene is a unidirectional ohmic conductor, the conductivity increasing steeply upon parallel alignment of the helices and decreases as the density of defects increases. Okahata et al. reported an increase in conductivity by three orders of magnitude after stress-aligning the duplexes in a film formed of salmon testes DNA.[11] From the materials and corrosion science perspective a chromosome is a fibrous binary alloy of AT and GC. In the normal, condensed resting state nuclear DNA is locally aligned. Structural analyses by X-ray diffraction, circular dichroism and electron and polarizing microscopies show that DNA is liquid crystalline in the chromatin of sperm nuclei of mammals, fish and arachnids, of bacteria and of protozoa. The duplexes are aligned in parallel in helical pre-cholesteric, cholesteric, smectic and columnar hexagonal liquid crystalline phases. DNA aligns spontaneously, forming liquid crystals also in vitro, when the weight fraction of DNA in evaporating solutions exceeds its weight fraction in nuclear chromatin.[12]

The accumulated oxidative damage to the protecting GC-rich domains is expected to affect the statistical likelihood of death or mutation of a cell under oxidative stress. Cathodic protection becomes ineffective upon exhaustion of the protective domain or upon its insulation from the protected domain. Thus, even if the damage to the sacrificial domain caused by a low flux of oxidants may only be transient, because it is likely to be excised and repaired, at a sufficiently high flux of oxidant the protective process will be overwhelmed and the protection of the essential domain will be disrupted. It is expected that upon transient or permanent exhaustion of the sacrificial domains, the frequency of those mutation that require scission at more than one point, such as translocations of long segments and telomer insertions, will increase particularly steeply.

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